Role of Wingless (Wg) signaling pathway in Aβ42 mediated neurodegeneration in Alzheimer's disease

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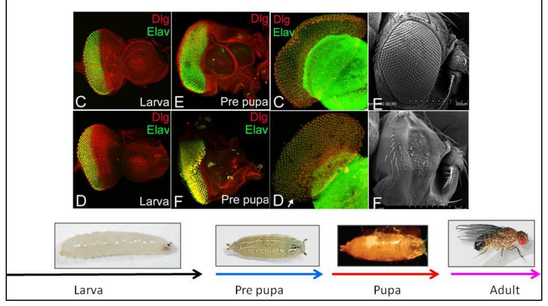
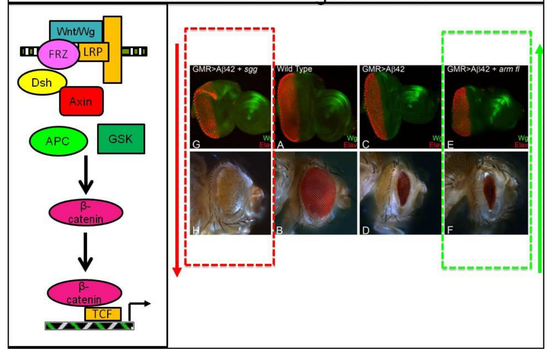
Abstract

Alzheimer's disease (AD), an age related progressive neurodegenerative disorder manifests as memory loss and reduced cognitive ability. One of the hallmarks of AD is formation of the Amyloid-beta (hereafter Aβ42) plaques, which initiates oxidative stress due to impaired signaling and finally leads to the death of neurons by unknown mechanism. However the exact mechanism causing cell death is still not well understood. We misexpressed high levels of human Aβ42 protein in the developing fly retina, which mimics AD like neuropathology. In a forward genetic screen we have identified members of highly conserved Wingless (Wg) signaling pathway as modifiers of the Aβ42 mediated neurodegeneration. Furthermore, Wg protein levels are upregulated in the dying cells marked by TUNEL staining. We have demonstrated that blocking Wg signaling pathway, by misexpressing negative regulator of Wg like Shaggy kinase (sgg) or a dominant negative form of Drosophila T-cell factor (dTCFDN5) or blocking Wg transport specifically by downregulating Porcupine (using porcupineRNAi) can rescue Aβ42 mediated neurodegeneration by reducing the number of dying cells and restoring the axonal targeting from the retina to the brain. We have developed a drug feeding regimen for flies and will test if we can use chemical inhibitors to block Wg signaling in neurons expressing high levels of Aβ42 and thereby prevent neurodegeneration in the Drosophila eye. We will test antagonists and agonist of Wg signaling to determine if they can work as chemical inhibitor/modifier of Aβ42 mediated neurodegeneration. The results from our studies will be presented.

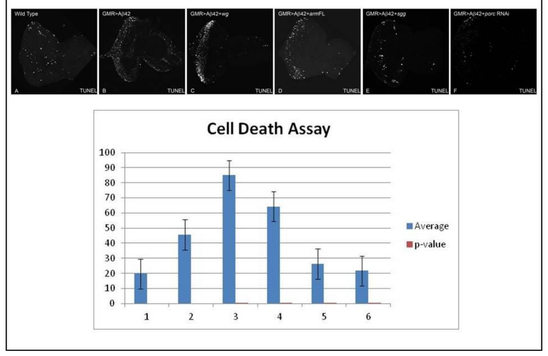
Misexpression of Aβ42 in fly eye by GMR-GAL4 exhibits progressive neurodegenerative phenotype



Blocking Wg Signaling suppresses the Aβ42 mediated neurodegeneration

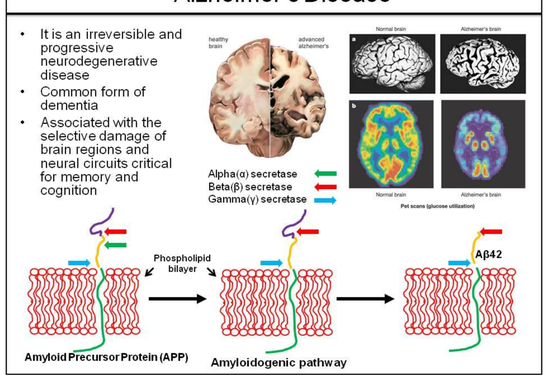


Cell Death Assay

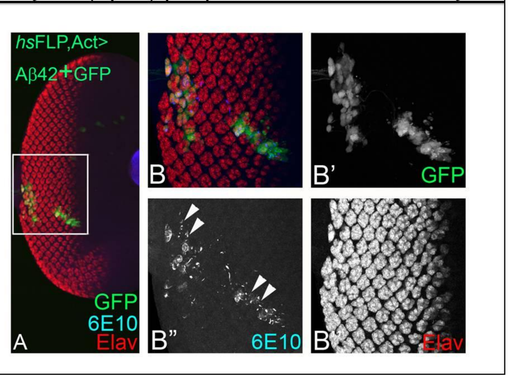


Alzheimer's Disease

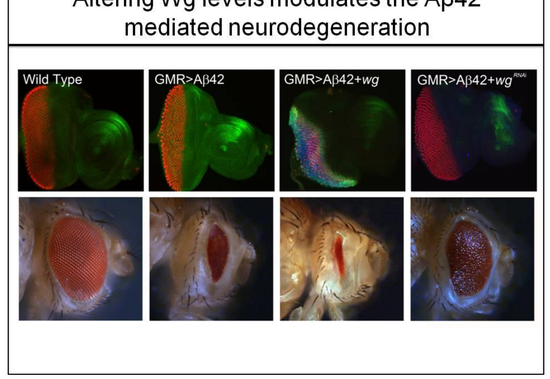
- It is an irreversible and progressive neurodegenerative disease
- Common form of dementia
- Associated with the selective damage of brain regions and neural circuits critical for memory and cognition



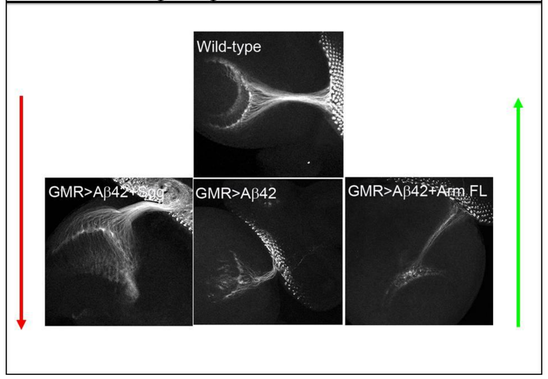
Amyloid (Aβ42) plaques are formed in the eye



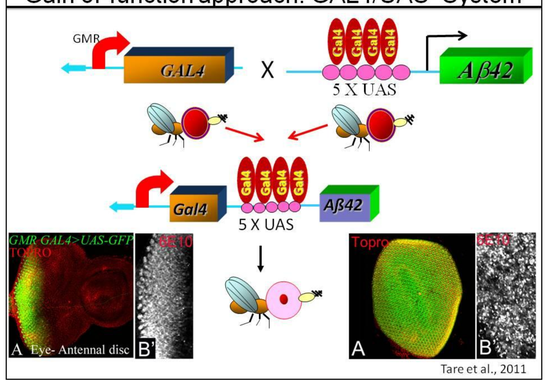
Altering Wg levels modulates the Aβ42 mediated neurodegeneration



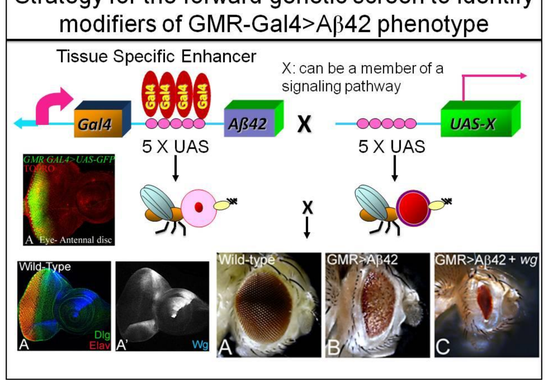
Axonal targeting from the retina to the brain



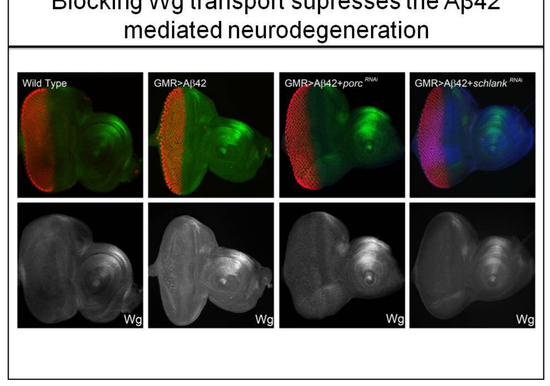
Gain of-function approach: GAL4/UAS- System



Strategy for the forward genetic screen to identify modifiers of GMR-Gal4>Aβ42 phenotype



Blocking Wg transport supresses the Aβ42 mediated neurodegeneration



Conclusion

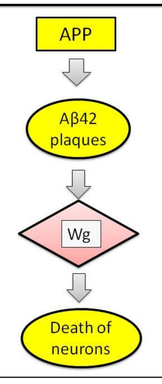
1) Activation of Wg Signaling triggers Aβ42 mediated neurodegeneration

2) Blocking Wg Signaling suppresses the Aβ42 mediated neurodegeneration

3) Wg signaling affects axonal targeting from the retina to the brain in Aβ42 background

4) Wg signaling triggers cell death in Aβ42 mediated neurodegeneration.

5) Blocking Wg transport suppresses the Aβ42 mediated neurodegeneration



Acknowledgement: We would like to thank the Bloomington Stock Center and DSHB for the reagents. This work has been supported in part by the University of Dayton Office for Graduate Academic Affairs through the Graduate Student Summer Fellowship Program.